# Pharmacologic Treatment of Spasticity in Children

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Many clinicians frequently face the dilemma of whether and how to medically treat spasticity. When pharmacologic intervention is deemed appropriate, treatment decisions must first be based on accurate assessment using valid and reliable clinical instruments, and, importantly, specific, measurable, achievable, and realistic treatment goals should be delineated. For the treatment of localized or segmental spasticity, botulinum toxin (BoNT-A) is recommended as an effective and generally safe treatment. For more generalized spasticity, a number of useful oral agents and intrathecal baclofen are available, each with their positive and negative attributes. Fundamental knowledge of pharmacologic properties and toxicities of these medications is required for safe and appropriate use. To achieve optimum results, spasticity treatment should be part of an integrated therapeutic approach in which patients, caregivers, therapists, physicians, and surgeons have an open and clear communication about the overall rehabilitation process of the patient. This review summarizes the current pharmacologic approaches to spasticity treatment in children, critically evaluating published studies in the context of established evidence-based criteria.
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The National Institutes of Health Task Force on Childhood Motor Disorders defined spasticity as a hypertonia in which one or both of the following signs must be present: (1) muscle resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement and/or (2) muscle resistance to externally imposed movement rises rapidly above a threshold speed or joint angle.[1] Spasticity often occurs as a manifestation of the upper motor neuron syndrome and is associated with enhanced stretch reflexes, released flexor reflexes in the lower limbs, loss of dexterity, and weakness.[2]

The most common cause of spasticity in childhood is cerebral palsy (CP).[3] CP affects 3.6 of every 1,000 8-year-old children in the United States.[4] Other causes of spasticity include traumatic brain injury, spinal cord injury, central nervous system tumor or infarct, metabolic disorders, and hydrocephalus.[5]

Many treatments have been proposed to treat spasticity under the assumption that spasticity is the main factor causing motor dysfunction and disability. Although there is evidence showing a clear relationship of spasticity and func-

tion,[6,7] a careful pretreatment assessment of the different components of the motor disorder should be performed to obtain accurate and objective information for patient selection and, ultimately, prediction of the direct response to treatment at the impairment and functional levels.

## Measurement of Spasticity

By definition, phasic spasticity is the increased muscle resistance to stretch that is velocity dependent. Thus, stretching a muscle at a sufficiently high velocity is essential to elicit a stretch reflex at a specific joint angle. Traditionally, in clinical practice as well as in scientific research, the Ashworth[8] and the "Modified" Ashworth[9] scales have been used to measure spasticity. These instruments report on a 5-point and 6-point scale, respectively, the resistance during passive muscle stretching at an unspecified velocity or body posture. It is now well established that these scales measure a broader set of neural and musculoskeletal factors of non–velocity-dependent hypertonia in addition to spasticity itself.[10,11] A clinical instrument more consistent with the definition of spasticity is the Tardieu Scale (TS).[12] The TS takes into account the joint angle measure at different velocities of joint movement providing 2 parameters: the spasticity angle (X), which is obtained by calculating the difference between the angle of arrest at slow speed and the angle of catch and release (or clonus) at fast speed, and the spasticity grade (Y) on a 5-point ordinal scale. Gracies et al[12] recently reported on the intra-

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and interrater reliability of the TS for assessing spasticity in children with CP. They found that after formal training, across all joints and parameters, intra- and interrater agreement rates were good to excellent, ranging from 74% to 90%.[12]

## Setting Goals for Treatment

Pediatric neurologists, developmental pediatricians, orthopedists, neurosurgeons, and physiatrists frequently face the dilemma of whether or not to treat spasticity. Reduction in spasticity may not always be desirable; some patients may experience a decline in function when spasticity is reduced.[13] Once it is determined that spasticity is present and that it has a detrimental effect on the patient's function, quality of life, care, and/or comfort, specific and measurable goals of treatment should be established. For treatment goals to be realistic, meaningful, and achievable, the patient, caregivers, and health care providers should be involved in this discussion. Periodic measurements of these goals will be required to determine progress. The Goal Attainment Scale (GAS) has been proven to be an effective clinical and research tool to measure progress in the treatment of children with spasticity.[14,15]

## Treatment of Focal/Segmental Spasticity

The following section addresses pharmacologic treatments for focal or segmental spasticity, including botulinum toxin (BoNT), phenol, and alcohol. Injectable therapy to prevent nerve-muscle transmission is known as chemodenervation, neurolysis, or neuromuscular blockade. Two strategies are in current use: perineural injection of phenol or ethyl alcohol and intramuscular injection of BoNT. Although the use of BoNT has grown exponentially and has substantially replaced phenol and alcohol, all 3 techniques are used for focal spasticity and addressing specific muscles in generalized spasticity. BoNT provides a specific presynaptic neuromuscular junction blockade but does not injure the nerve or muscle. Phenol and alcohol are effective by providing neural and, at times, muscle destruction. The common denominator of these medications is the blockade of the agonist muscles allowing increased stretch and resting length while the antagonist muscles continue activity and strengthen. The goal is a more appropriate balance between the agonists and antagonists with prolonged improvement.[16]

### Alcohol and Phenol

Alcohol and phenol have had a historic role in the care of children with hypertonia. Phenol is typically injected at a concentration of 3% to 6% aqueous solution, whereas absolute alcohol is diluted to 30% to 50%. Electrical stimulation is required to identify the target nerve. The procedure is poorly tolerated in children and requires sedation or anesthesia. The agent is injected perineurally, where it promotes denervation via axonal degeneration. The direct muscle effects of phenol relate to the neurogenic atrophy as well as local necrosis of the muscle. Functional reinnervation occurs over months to years. Adverse effects of both agents include a significant risk of long-term pain or paresthesia when targeting a mixed motor and sensory nerve. Thus, the technique is best used when focusing on exclusive motor nerves. The potential complications and the requirement for the advanced technical skills for appropriate administration have kept phenol and alcohol from assuming a larger role in focal spasticity management. Although some studies have shown the benefit for spasticity in CP of both alcohol[17] and phenol,[18,19] none of the studies reached the criteria to be included in the recent American Academy of Neurology (AAN) practice parameter on pharmacologic treatment of spasticity in children and adolescents with CP.[20] The recommendation for these 2 medications was level U, indicating that there are insufficient data to support or refute the use of phenol or alcohol. (For a review of the classification grades for evidence and recommendations from the practice parameter, please see Appendices 1 and 2.)

### BoNT

BoNT is an exotoxin produced by clostridium botulinum. There are 7 naturally occurring serotypes of the toxin, A through G, all of which are zinc proteases that target the cholinergic presynaptic vesicle fusion at the neuromuscular junction, decreasing the release of acetylcholine and causing denervation. Serotypes A and B are commercially available. BoNT-A is marketed under the tradenames Botox (Allergan, Irvine, CA) and Dysport (Ipsen, Paris, France) in the United States and Xeomin (Merz, Frankfurt, Germany) in Europe. BoNT-B is marketed by Solstice Neuroscience (Malvern, PA) as MyoBloc in the United States and NeuroBloc in Europe. Types A and B have a similar duration of clinical action of approximately 3 months. Potency is expressed in terms of mouse units, the amount of toxin required to kill 50% of mice in a standardized assay. It is important to note that the potency of a single unit varies greatly among the commercial types. Although the potency of 1 U of Botox is roughly equal to 1 U of Xeomin, 3 U of Dysport, and 40 to 50 U of MyoBloc, it is very important to recognize that a simple ratio of dosing equivalencies cannot be applied. It is critical to be cognizant of the commercial brand when interpreting the literature or considering dosing recommendations for clinical care.

Most published research in CP has been done with BoNT-A although a small number of studies have examined the effect of BoNT-B in this population.[21] BoNT-B and BoNT-A have both been combined successfully with phenol injection, allowing an increase in the number of treated muscles per injection session.[22] BoNT-B has a tendency to cause more autonomic side effects than BoNT-A and should be used with this caution in mind.[23] In the recent AAN practice parameter review, none of the articles met criteria for inclusion. As a result, the recommendation for BoNT-B is level U, indicating that there are insufficient data to support or refute the use.[20]

In the same practice parameter, a total of 148 studies using BoNT-A to reduce spasticity in children with CP met eligibility criteria, with 15 studies rising to class I and 5 to class II.

Spasticity reduction was reported in all but 3 studies.[24-26] Analysis revealed that spasticity reduction was statistically significant at 2 weeks,[27] 4 weeks,[28] and 3 months[29] after treatment.

One third of these studies assessed the effect of BoNT-A in the upper extremity.[24,29-32] One study showed that upper-extremity injections of BoNT-A plus occupational therapy was superior to occupational therapy alone on the Quality of Upper Extremity Skill Test,[30] an effect the authors correlated with preinjection grip strength.[33] Statistical significance was reached at 1 month, but when a similar class I study delivered the medication guided by electrical stimulation, the effect was significant at both 1 and 3 months.[31]

Although earlier studies of BoNT-A concentrated mainly on showing spasticity reduction via lowered Ashworth scores, more recent interest has been focused on determining the functional benefit from injections. A class I study has shown, based on 3-dimensional gait analysis, that a high-dose group compared with low-dose group had greater efficacy of foot dorsiflexion and a longer duration of effect.[34] Significant functional improvement has been documented by the use of the Gross Motor Function Measure (GMFM) Walking Dimension, the Physician Rating Scale, and the GAS.[35,36] Additionally, the GMFM and PRS remained statistically significant at 12 weeks.[35] In contrast, 3 class I placebo-controlled studies using the same BoNT-A preparation and slightly higher doses (n = 64,[26] n = 125,[37] and n = 52[38]) did not show a functional improvement by GMFM despite a reduction in spasticity evidenced by improved ankle dorsiflexion. It is common practice to use BoNT-A in combination with serial casting, orthoses, and physical and occupational therapy.[32]

Dosing guidelines for Botox for adults and children have been developed by consensus. The recommended ceiling doses used by experienced injectors have increased from the initial recommendation of 4 U/kg to greater than 20 U/kg in specific cases. In the pediatric population, the dose should be based on the child's weight, muscle bulk, and degree of spasticity. An effective dose with an injection interval of at least 3 months or more is recommended to minimize the risk of antibody development. Children may benefit from a topical anesthetic, anxiolytic, or light sedation during injection. Although the clinical examination is sufficient for determining the contributing muscles in many situations, electromyography, electrical stimulation, and ultrasound are used to help target difficult-to-localize muscles. Repeated exposures to BoNT can lead to immunoresistance. Although it is possible to switch serotypes, immunoresistance to the second may develop more quickly than to the first.

Adverse effects of BoNT-A injections are usually mild and transient, consisting of pain at the injection site, fatigue, and occasional incontinence and dysphagia. Excess weakness, although rare, has been described and has led to significant warnings of which patients and clinicians must be aware. On April 30, 2009, the US Food and Drug Administration announced that safety label changes, including a boxed warning and a Risk Evaluation and Mitigation Strategy, are necessary for all BoNT products. As stated in the new release: "The

agency said it took the action because of reports that the effects of the BoNT may spread from the area of injection to other areas of the body, causing symptoms similar to those of botulism, including unexpected loss of strength or muscle weakness, hoarseness or trouble talking, trouble saying words clearly, loss of bladder control, trouble breathing, trouble swallowing, double vision, blurred vision and drooping eyelids." The symptoms have been primarily reported in children with CP treated for muscle spasticity. Adults have also experienced these symptoms when treated both for approved and unapproved uses. The release stated that health care professionals who use BoNTs should do the following:

1. Understand that dosage strength (potency) expressed in "units" is different among the BoNT products; clinical doses expressed in units are not interchangeable from one product to another.
2. Be alert to and educate patients and caregivers about the potential for effects after the administration of BoNTs, such as the unexpected loss of strength or muscle weakness, hoarseness or trouble talking, trouble saying words clearly, loss of bladder control, trouble breathing, trouble swallowing, double vision, blurred vision, and drooping eyelids.
3. Understand that these effects have been reported as early as several hours and as late as several weeks after treatment.
4. Advise patients to seek immediate medical attention if they develop any of these symptoms.

Also, the names of the medications were clarified as onabotulinumtoxin A for type A marketed as Botox (Allergan), abobotulinumtoxin A for type A marketed as Dysport (Ipsen Biopharm, Ltd), and rimabotulinumtoxin B for type B marketed as Myobloc (Solstice Neuroscience Series).

The recent AAN practice parameter found that for children with CP, BoNT-A is established as an effective treatment to reduce spasticity in the upper and lower extremities (Class I and II evidence), but there is conflicting evidence regarding functional improvement. The available evidence suggests that BoNT-A is generally safe in children with CP. However, severe generalized weakness may occur. It was concluded that in localized or segmental spasticity, BoNT-A "should be offered as an effective and generally safe treatment."[20] Although this rose to a level A (should be done) recommendation, the evidence for its use in motor function was insufficient to support or refute its use. Overall, the recommendation was that BoNT-A should be offered as an effective and generally safe treatment for localized/segmental spasticity in the upper and lower extremities of children with CP that warrants treatment. This is further supported by the recently published evidence-based review on the safety and efficacy of BoNT-A for the treatment of adult and childhood spasticity. The evidence supported the use of BoNT-A as a treatment of spasticity in the lower extremities (level A) and for the treatment of spasticity in the upper extremities (level B) of children with CP.[39]

# Treatment of Generalized Spasticity

The following section addresses pharmacologic treatments for generalized spasticity including oral/enteral agents and intrathecal baclofen.

## Oral/Enteral Medications

For individuals who have generalized spasticity, oral or enteral medications can provide systemic symptom relief. Advantages include the relative ease of use and the lower cost compared with other interventions, but each of these drugs carries with it risks of side effects and a fairly limited base of research on therapeutic efficacy in children.

### Baclofen

Baclofen, a GABA$_B$ receptor agonist, is widely used for adults with spasticity associated with spinal cord injury. The precise mechanism of its action is not well described but may include inhibition of spinal reflexes as well as supraspinal effects. The pharmacokinetics of baclofen are inadequately described for pediatric populations[40] despite common usage to reduce spasticity and muscle spasms in children with generalized spasticity. Dosing parameters are generally based on expert opinion and are quite variable.[41] Typical practices include starting at a low dose (2.5-5 mg daily) and titrating the dose up for maximum clinical benefit without excessive sleepiness, confusion, hypotonia, or other side effects. Maximum doses in children and adolescents vary from 40 to 80 mg daily in 3 or 4 divided doses.[42] If baclofen is discontinued, the dose should be gradually reduced to avoid a withdrawal syndrome that may include exacerbation of spasticity, hyperthermia, altered mental status, and seizures.[43]

Evidence is limited and conflicting regarding baclofen's effect for children. One double-blind crossover trial revealed reduced spasticity and improved range of motion in children with CP on baclofen versus placebo,[13] whereas another crossover trial found improvement in GAS scores but not in spasticity or scores on the Pediatric Evaluation of Disability Inventory.[14] Recent guidelines concluded that there is insufficient evidence to support or refute the use of baclofen for spasticity or functional impairment in childhood CP.[20]

### Tizanidine

Tizanidine's mechanism of action is central alpha-2 noradrenergic agonist activity to reduce spasticity. Effects include reduced muscle stretch reflexes, greater presynaptic inhibition, and modest reduction in blood pressure. Data in adults with spasticity related to spinal cord injury and multiple sclerosis show tizanidine's amelioration of spasticity,[44] but data in children are scarce. Pharmacokinetics of tizanidine are not described in children, but a half-life of about 2.5 hours and linear pharmacokinetics are described in adults. Metabolism of tizanidine may be affected by liver dysfunction. The most common side effects of tizanidine are dry mouth, fatigue, sleepiness, dizziness, hypotension, and hepatotoxicity although clear data on adverse events in children are not available. Sedation may be a beneficial side effect if

tizanidine is being used to improve spasms and comfort at night. With a reported half-life of only a few hours, tizanidine usually requires frequent dosing for sustained control of spasticity, but no dosing guidelines are reported for children.

Two studies report outcomes of tizanidine treatment in children with CP. One study found that Russian children with diparetic CP showed improved motor ability.[45] A small placebo-controlled parallel study showed spasticity reduction, but no functional measures were used.[46] With these limited evaluations, the AAN practice parameter recommends that tizanidine be considered for the treatment of spasticity in childhood CP, but the evidence was deemed insufficient to comment on effects on function.[20]

### Diazepam

Diazepam is a benzodiazepine that acts postsynaptically on GABA$_A$ receptors. Similar to other spasticity medications, data on efficacy and pharmacokinetics are wanting although a half-life of up to 18 hours has been reported. Dosing regimens vary as well, with total doses ranging from 0.5 to 15 mg or 0.12 to 0.8 mg/kg daily and usually divided into a few doses. Diazepam is recognized to cause significant sedation, which may be useful to aid sleep.[47] Other possible side effects include weakness, ataxia or dyscoordination, and hypersalivation. Of concern as well, diazepam can produce tolerance and dependence so that monitoring by a professional is necessary for long-term use or to facilitate discontinuation.[43] Diazepam has been investigated in several studies involving children with spasticity. In a randomized trial, diazepam was superior to placebo in tone reduction and range of motion, but no functional outcome measures were explored.[48] Other studies did not use standardized functional outcome measures either but showed better spasticity relief than dantrolene or placebo (and superior effects with diazepam and dantrolene in combination)[49] or better behavior and coordination than placebo.[50] The available evidence has led to an AAN practice parameter recommendation that diazepam be considered for treating spasticity in children with CP, but, again, no recommendation was made regarding effects on function.[20]

### Dantrolene Sodium

Dantrolene sodium is unique among the antispasticity medications because it acts peripherally rather than centrally. Dantrolene sodium uncouples excitation and contraction in muscles by inhibiting calcium release at the sarcoplasmic reticulum. The pharmacokinetics of dantrolene sodium has not been reported for children. Dosing strategies include incremental increases in the dose beginning at as little as 12.5 mg daily and increasing to as much as 12 mg/kg or 400 mg daily in divided doses depending on the effects. The major side effects are weakness and hepatotoxicity. Serious, irreversible liver failure is a risk with dantrolene sodium[51] although it has not been reported in children with spasticity. Regular monitoring of liver function is recommended before and during therapy with dantrolene sodium. Two well-designed studies had contrasting findings for dantrolene sodium, with one showing no effect on spasticity or function[52] and the other showing beneficial effects on tone, daily living skills, and movement control.[53] In clinical studies, side ef-

fects were frequent, including weakness, fatigue, irritability, drowsiness, anorexia, vomiting, diarrhea, and seizures. With the conflicting findings, the AAN practice parameter indicated the evidence is insufficient to support or refute the use of dantrolene sodium for children with CP.[20]

Oral/enteral medications for spasticity have attendant risks and may have unpleasant side effects. Nonetheless, these agents may be attractive as a convenient initial treatment, as a means to help with sleep, and/or in combination with focal treatments for spasticity in children. When more pronounced effects on generalized spasticity are desired, intrathecal baclofen offers a different mechanism for systemic treatment.

## Intrathecal Baclofen

Intrathecal baclofen therapy (ITB) involves the delivery of baclofen directly to the intrathecal space using a catheter that is attached to an implanted, refillable pump. When administered in this fashion, baclofen induces spasticity reduction at doses far lower than those required for clinical effect with an oral/enteral delivery mechanism.

Because ITB requires surgical implantation and carries with it a moderate risk of complications, careful screening is important. Test doses of baclofen delivered via lumbar puncture or temporary catheter are recommended for potential recipients. After pump placement, dose adjustments (via telemetry) are necessary for at least the first few months to ensure optimal clinical effect. Additionally, transcutaneous refills are required throughout treatment. Complications may involve overdosing, underdosing with or without withdrawal, catheter malfunction, wound infections, or fluid collections around the pump and occur at varying rates but may be more frequent in younger patients or those with greater spasticity.[54]

Baclofen withdrawal is a serious and potentially fatal situation[55] that may occur if a refill is not achieved at the appropriate interval or through unforeseen complications, such as pump or catheter malfunction. Symptoms of withdrawal include itching, exacerbated spasticity, blood pressure alterations, altered mental status, fever, rhabdomyolysis, and seizures. If intrathecal baclofen delivery cannot be immediately restored, withdrawal may be ameliorated with oral or enteral baclofen, intravenous benzodiazepines, dantrolene sodium, and/or cyproheptadine, but these interventions may not always be efficacious.

ITB has been fairly well evaluated for use in children with CP, including demonstration of spasticity reduction[56-60] and some functional improvements.[61,62] Although ITB is expensive, cost-effectiveness analysis was favorable.[63] At present, evidence is considered insufficient to support or refute the use of ITB for spasticity in children with CP.[20]

## Conclusions

Spasticity treatment cannot be performed in isolation without careful evaluation of other associated positive and negative impairments that result in obligatory and compensatory motor behaviors. The treatment of spasticity requires its proper identification and measurement by a valid and reliable instrument that can be used in the clinic (eg, TS). Specific, measurable, achievable, and realistic treatment goals should be in place before any antispasticity medication is started, taking into consideration the overall rehabilitation process of the patient as defined by the International Classification of Functioning, Disability and Health-Child and Youth.[64] For the treatment of focal spasticity, BoNT-A is recommended; for regional spasticity, ITB can be used; and for generalized spasticity, different oral agents are available. Good knowledge of pharmacologic properties and toxicity is necessary for proper use. For best results, spasticity treatment should be part of an integrated therapeutic approach in which patients, caregivers, therapists, physicians, and surgeons have an open and clear communication about the overall rehabilitation process of the patient.

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# Appendix 1

## Classification of Evidence for Therapeutic Intervention From the AAN Practice Parameter: Pharmacologic Treatment of Spasticity in Children and Adolescents With CP (an Evidence-Based Review): Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society.[20]

Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
  The following are also required:
  A. Concealed allocation
  B. Primary outcome(s) clearly defined
  C. Exclusion/inclusion criteria clearly defined
  D. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.
  E. For non inferiority or equivalence trials claiming to prove efficacy for 1 or both drugs, the following are also required:*
    1. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.
    2. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (eg, for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective).
    3. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
    4. The interpretation of the results of the study is based on a per protocol analysis that takes into account dropouts or crossovers.

Class II: A randomized controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks 1 criteria A-E above or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets B-E above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population in which outcome is independently assessed or independently derived by objective outcome measurement.

Class IV: Studies not meeting class I, II or III criteria, including consensus or expert opinion.†

# Appendix 2

## Classification of Recommendations From the AAN Practice Parameter: Pharmacologic Treatment of Spasticity in Children and Adolescents With CP (an Evidence-Based Review): Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society[20]

A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least 2 consistent class I studies.*)
B = Probably effective, ineffective, or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least 1 class I study or 2 consistent class II studies.)
C = Possibly effective, ineffective, or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least 1 class II study or 2 consistent class III studies.)
U = Data inadequate or conflicting given current knowledge; treatment (test, predictor) is unproven.

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*Note that Numbers 1 to 3 in class are required for class II in equivalence trials. If any one of the 3 are missing, the class is automatically downgraded to class III.
†Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, or investigator) expectation or bias (eg, blood tests and administrative outcome data).
*In exceptional cases, one convincing class I study may suffice for an "A" recommendation if (1) all criteria are met, (2) the magnitude of effect is large (relative rate improved outcome >5 and the lower limit of the confidence interval is >2).